

Instructional lecture

The osteoporosis revolution marches on

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Introduction

In 1997, when I reported on the progress of the “osteoporosis revolution,”¹ five topics were emphasized: genetics, local factors, bone mass measurements, biochemical markers, and prevention and therapy. During the past 10 years there has been substantial progress in all of these areas, but the revolution is by no means over. This review summarizes our current concepts of epidemiology, pathogenesis, diagnosis, prevention, and treatment with an emphasis on the advances that have been made during the past decade.

The osteoporosis revolution is a relatively recent problem in human history, due largely to the great increase in life expectancy and the effects of “civilization,” that is, the movement of humans from outdoors to indoors and from heavy physical activity to sedentary occupations. Although originally the diagnosis of osteoporosis was made after patients had had a fragility fracture, we now can make a diagnosis of osteoporosis before fractures occur when there is a marked reduction of bone mineral density (BMD) or of osteopenia, when there is a moderate reduction in BMD. This has made it possible to start preventive measures and early therapy in high-risk patients before there is any fracture. Nevertheless, most patients are not diagnosed until after their first fragility fracture; and, unfortunately, many are not diagnosed or treated even after that fracture. Although the highest incidence is among postmenopausal women, substantial numbers of older men are affected; and a few younger individuals, particularly those with important secondary causes for bone loss, are also at risk for fragility fractures.

Epidemiology

Osteoporosis is a common disorder. There were approximately 2 million fragility fractures in the United States in 2005, and this number will increase to 3 million by 2025 unless we institute more effective preventive measures.² Similar figures have been reported for most developed countries.³ In the United States, about half of these fractures occur in patients with a sufficiently low bone mass to warrant the diagnosis of osteoporosis (i.e., more than 2.5 SD below the young adult mean), and the other half occur in patients with osteopenia (i.e., BMD of -1.0 to 2.5 SD). The most common fragility fractures are of the proximal femur, lower thoracic and lumbar vertebrae, and distal radius. However, fragility fractures can occur in many other sites. Although the absolute incidence of fragility fractures is increasing rapidly, largely because of greater longevity, a number of studies have suggested that age-specific rates are decreasing in some countries, perhaps due to greater recognition of the problem and greater attention to bone health. The U.S. Surgeon General made this the subject of a major report on “Bone Health and Osteoporosis.”⁴ The World Health Organization, which established the present diagnostic criteria, is making a major effort to redefine osteoporosis in terms of absolute fracture risk and establish better approaches to diagnosis and prevention.

Pathogenesis

Our basic concepts of the pathogenesis of osteoporosis have not changed greatly during the last decade, but some new pathways have been identified.⁵ The four basic mechanisms are (1) failure to achieve optimal peak bone mass and strength during growth and development. This is largely determined by genetics but is also contributed to by nutrition and lifestyle. (2)

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Increased bone resorption with aging, particularly after menopause. This is largely due to estrogen deficiency but may be enhanced by calcium and vitamin deficiency producing secondary hyperparathyroidism. An increase in inflammatory cytokines may play a role. (3) Inadequate bone formation during remodeling. This is probably due to age-related impairment of osteoblastic cell renewal and function and to changes in specific growth factors. (4) Increased propensity to fall. This occurs because of neural and muscular impairment with aging as well as the increasing number of drugs given to the elderly for other disorders that can impair balance or perception.

Genetics

There have been remarkable advances in our understanding of the genetic determinants of bone mass and strength.⁶⁻⁸ Perhaps the most important has been identification of the Wnt signaling pathway.⁹ Activation of Wnt signaling in bone results in increased bone formation and probably in decreased resorption. The pathway also has an effect on early precursor cells to direct them to the osteoblastic lineage rather than to adipocytes or cartilage cells. Activating mutations of lipoprotein-related receptor-5 (LRP-5), which is part of the receptor complex for Wnt ligands, produce a high bone mass phenotype.⁹⁻¹¹ Deletion of LRP5 produces severe osteoporosis.¹² A high bone mass phenotype also occurs when inhibitors of this pathway, sclerostin or dickkopf (DKK),¹³ are deleted. The potential role of polymorphisms in the multiple proteins involved in this complex regulatory system are just beginning to be explored and could account for genetic differences in bone mass and strength.

Other findings point to a possible role of abnormalities of collagen in osteoporosis, particularly polymorphisms of the $\alpha 1$ collagen gene, which are associated with increased skeletal fragility.¹⁴ This and other findings call into question the concept that there are no biochemical abnormalities of the matrix in osteoporosis. Subtle abnormalities may indeed exist and contribute to fragility. Many other candidate genes have been analyzed, all of which appear to contribute relatively small effects on bone mass and fragility but which in combination could be important determinants of fracture risk as well as the response to therapy.¹⁵ Moreover, interactions between genetics and environment may modify these effects.¹⁶

Nutrition and lifestyle

Our hunter-gatherer and agricultural ancestors probably had stronger bones. This could be due not only to a

direct effect of physical activity but to greater nutrient intake, particularly of calcium, associated with this activity, as well as greater sun exposure and hence higher levels of vitamin D.¹⁷ These factors may be of particular importance during childhood and adolescence, when peak bone mass is developed. Many studies indicate that gains in bone mass can be achieved by improving physical activity and nutrition, but most also show that these gains are lost when the program is discontinued.¹⁸ In addition to calcium and vitamin D, protein intake and vitamin K may be critical for achieving bone mass and strength.¹⁹ Other nutritional interventions have been explored, such as changes in the proportion of saturated and unsaturated fats or in omega-3 fatty acids, but the data are limited.^{20,21}

Accelerated bone resorption

Although it is clear that estrogen deficiency results in accelerated bone resorption at any age, the precise mechanisms have still not been established.⁵ Moreover, there may be separate effects of androgens and other hormones involved in gonadal regulation such as follicle-stimulating hormone (FSH) or inhibin.²²⁻²⁴ Recent studies indicate that estrogen may act at multiple sites — on both the hematopoietic precursors of the osteoclasts and the osteoblast-osteoclast interaction that regulates bone resorption. Thus, estrogen administration can decrease bone resorption by decreasing the ability of marrow cells to respond to stimulation by receptor activator of NF κ B (RANKL) and by decreasing the expression of RANKL in marrow cells.^{25,26} We are still not sure whether the RANKL-expressing cells that are affected by estrogen are entirely from the osteoblast lineage or include members of the lymphocyte family. In any event, the production of bone-resorbing cytokines may mediate this response.²⁷⁻³¹ Of great interest is the observation that the amount of estrogen required to affect bone in postmenopausal women may be substantially less than that required to affect the classic target organs, such as the breast or uterus, although this may not be the case in rodents.^{32,33} Fracture risk is highest in both men and women with the lowest estrogen levels, and doses of estrogen that are one-quarter or less of the usual doses that are given at menopause can prevent bone loss. Because of the recent data indicating that with higher doses of estrogen the costs may outweigh the benefits, the exploration of ultra-low-dose estrogen for prevention and treatment of osteoporosis is quite attractive. Large studies are required to determine if these low doses actually do have less risk and are effective in reducing fractures.

Low intake of calcium and low levels of vitamin D are quite common in the elderly population at risk for osteo-

porosis.³⁴ These conditions aggravate bone loss by producing secondary hyperparathyroidism and increased bone resorption; and they may also have adverse effects on muscle strength and physical performance and thus increase the risk of falls.^{35,36} Recent studies have suggested that vitamin D requirements for optimal health may be much higher than the usually recommended levels. Because the sun does not activate vitamin D formation in the skin in northern latitudes during the winter, supplementation is important. Moreover vitamin D insufficiency is still quite common in equatorial regions, probably because the individuals cover themselves and avoid sun exposure. There is still debate concerning the optimal levels of vitamin D, but a daily intake of 2000 U or even more appears to be quite safe.^{17,36}

Inadequate bone formation

During childhood and adolescence the skeleton maintains remarkably high rates of bone formation for the modeling of new bone and for remodeling. Thus, rates of bone resorption much higher than those encountered in patients with osteoporosis can occur in the presence of substantial bone gain. At some point shortly after peak bone mass has been achieved, this capacity for high rates of bone formation diminishes and the amount of new bone in remodeling sites on the trabecular bone surfaces (mean wall thickness) progressively decreases.³⁷ Trabecular bone and, to a lesser extent, cortical bone mass probably begin to decrease at some sites when people are in their twenties, long before the major hormonal changes of menopause or aging.³⁸ However, sex hormones may still play a role in the changes in bone of younger individuals.^{39,40}

The reasons for the age-related decrease in bone formation are not well understood. It is possible that after multiple replications the precursor cells of the osteoblastic lineage gradually lose their capacity to replicate and differentiate. The changes in bone mass during this period are extremely variable, and it is also possible that individuals destined to become osteoporotic are the ones who show the greatest impairment of bone formation as younger adults.^{41,42} This may be due to changes in growth factors. Many growth factors affect the skeleton, including insulin-like growth factor-1, fibroblast growth factor, vascular endothelial growth factor, bone morphogenetic proteins (BMPs), transforming growth factor- β , and prostaglandins.^{43–48} Moreover, cytokines can inhibit formation as well as stimulate resorption.⁴⁹ Polymorphisms in the genes for some of these factors have been implicated as determinants of bone mass and fracture risk.^{50,51}

The role of the Wnt signaling pathway in the pathogenesis of osteoporosis has not yet been fully defined.⁵²

The clinical findings of increased bone mass due largely to increased bone formation in patients with increased activity of this pathway as well as the finding of severe osteoporosis in the LRP-5-deficient osteoporosis pseudoglioma syndrome, make it reasonable to look for smaller variations in Wnt signaling as a mechanism for impaired bone formation in osteoporosis. The regulation of this pathway is complex, and there are many sites at which abnormalities could occur, including not only the inhibitory proteins such as sclerostin, secreted frizzled related protein, and dickkopf but also Wnt ligands and the LRP-5 and frizzled receptors themselves.^{53,54} Polymorphisms of LRP-5 have been associated with differences in bone mass and fracture incidence.⁵⁵ Moreover, mutations in LRP-5 have been described in children with primary osteoporosis.⁵⁶ This possibility is reinforced by the observation that the most effective current anabolic agent, intermittent PTH, appears to act at least in part by reducing sclerostin, presumably leading to activation of Wnt signaling.^{11,57–59} One feature of the Wnt pathway that is of particular interest is the observation that not only does activation increase bone formation, it may also decrease bone resorption and decrease the propensity for precursor cells to differentiate into adipocytes.

Another exciting new area that may be relevant to the pathogenesis of osteoporosis is the evidence that bone formation is under neural control. Effects of leptin mediated by the central nervous system and peripheral effects of both the β -adrenergic and the cannabinoid systems have been implicated in regulation of the skeleton.^{60–62} Moreover, an effect of β -blockers on bone density and fractures has been reported, although the results are not entirely consistent.⁶³

Diagnosis of osteoporosis and assessment of fracture risk

Although the use of BMD for diagnosing osteoporosis has been broadly applied during the last two decades, a new approach in which BMD and other risk factors are used together to estimate true absolute fracture risk is rapidly being developed and likely to replace the use of BMD alone, with its arbitrary diagnostic cutoffs.⁶⁴ Currently, the factors that are most frequently used to assess fracture risk are age, family and personal fracture history, body weight, and the presence of aggravating disorders such as rheumatoid arthritis. The use of biochemical markers of bone turnover to refine this assessment has not yet become established, even though there is good evidence that high turnover is associated with increased fracture risk.⁶⁵ One reason for the uncertainty concerning the use of biochemical markers is the lack of uniformity in their assay measurements.⁶⁶

An important advance that is under development, but likely to be widely available in the next decade, is assessment of the microarchitecture of the skeleton. It is now possible to assess trabecular structure and measure such important properties as trabecular spacing and the relative proportion of rods and plates using either high-resolution computed tomography (CT) or magnetic resonance imaging (MRI), but these procedures are still not at the stage of general clinical application.^{67,68}

One critical aspect of diagnosis is the appropriate workup to rule out important secondary causes of bone loss and fragility.⁶⁹ A number of cost-effective stepwise approaches have been described, but they are not being applied in most cases.

Genetic diagnosis, except for the severe forms of skeletal fragility that we term osteogenesis imperfecta, is not yet a clinically useful option. However, it seems likely that in the future, when a substantial number of genetic polymorphisms that impinge on bone mass and strength have been identified, a genetic profile could be developed that would greatly enhance the assessment of fracture risk.

Prevention and treatment

There have been substantial advances in the orthopedic management of fragility fractures that have reduced morbidity and mortality and shortened the time to recovery, but they are beyond the scope of this review. The concept of fracture prevention is central to medical treatment of osteoporosis. The goal of treatment is to reduce fracture risk (i.e., prevent future fractures). There has been increasing emphasis on a lifelong approach to this goal.⁴ Improved bone health in children, particularly in adolescents during the rapid growth spurt, through better nutrition and exercise might have a substantial effect on the risk of fractures later in life. These same bone health measures are critical for any therapeutic program in older individuals who have moderate to severe bone loss. In many of these patients, however, pharmacotherapy is also indicated. Ten years ago the most widely used agents were estrogens; but with the evidence from the Women's Health Initiative that the risks of estrogen in terms of cardiovascular disease and breast cancer might outweigh the benefits, this use has decreased.⁷⁰ Hence, bisphosphonate therapy has become the preferred approach.^{71,72}

Large clinical trials have demonstrated the antifracture efficacy of bisphosphonates, but they are far from ideal drugs. When given orally only 1% or less of the dose is absorbed, and variations of this absorption are likely to alter efficacy. There are also side effects, particularly with oral administration, that limit their use; furthermore, fracture reduction averages only about

50%. Intravenous bisphosphonates are being developed. For zoledronic acid, there is recent evidence of substantial antifracture efficacy when given as a single infusion once a year for 3 years.⁷³ One concern is that we still do not know the long-term safety of bisphosphonates.⁷⁴

During the past decade there has also been increasing use of a selective estrogen receptor modulator (SERM), raloxifene.⁷² Efficacy has been demonstrated, but only for vertebral fractures. Newer SERMs are being tested and may show greater clinical efficacy. Another approach that deserves further exploration is the use of ultra-low-dose estrogen. This might avoid the adverse effects of therapy and has been shown to increase bone density, but it has not yet been tested for fracture efficacy.^{75,76}

Calcitonin is an antiresorptive agent, but its efficacy in the treatment of osteoporosis remains uncertain.^{71,72,77}

A number of other antiresorptives are currently under study.⁷⁸ They include the use of an antibody to RANKL, which blocks its interaction with RANK and rapidly reduces bone resorption. Injections of this antibody can maintain decreased resorption rates for 6 months and increase BMD as effectively as bisphosphonates.⁷⁹ Direct inhibition of osteoclast activity by blocking acid secretion, inhibiting cathepsin K, or interfering with the adhesion of osteoclasts via integrin receptors are also being explored.⁸⁰⁻⁸²

The relative effects of antiresorptive therapy are similar in patients with mild or severe osteoporosis; in the latter, the fracture rate of remains quite high, so many patients might be regarded as therapeutic failures. In addition some patients continue to lose BMD on antiresorptive therapy. As yet, there is no evidence that changing from one antiresorptive to another has any benefit, although intravenous therapy might be considered in patients who do not absorb or do not tolerate oral bisphosphonates. It is in these patients that anabolic therapy is most often considered.

Anabolic therapy

That low doses of parathyroid hormone given intermittently could increase bone mass was demonstrated in experimental animals more than half a century ago. However, the clinical application of this effect was achieved only in the last decade.^{83,84} Daily subcutaneous administration of synthetic 1-34 parathyroid hormone (teriparatide) was found to increase bone density and reduce fracture risk, not by inhibiting resorption but by stimulating both resorption and formation, with a greater formation effect, thus resulting in increased bone mass. This may be related to decreased sclerostin or increased insulin-like growth factor-2 production.^{57,85}

The new bone formed is structurally sound, in contrast to the earlier studies using sodium fluoride, which increased bone mass but also increased fragility at higher doses.⁸⁶ Teriparatide has been shown to be effective in both men and women and in patients with glucocorticoid-induced osteoporosis. One concern has been that its initial efficacy may be reduced in patients who are treated with bisphosphonates.⁸⁷ However, teriparatide still increases bone density in such patients.⁸⁸

Although teriparatide is effective, its use has been limited by the inconvenience of daily injection as well as the high cost. Alternatives to injection of teriparatide are being explored, including administration by nasal spray⁸⁹ or the use of “calcilytic” agents that interfere with the calcium receptor and produce a transient increase in endogenous parathyroid hormone (PTH) secretion.⁹⁰ Prostaglandins have been shown to increase both bone resorption and formation with a net increase in bone mass in animals.⁹¹ Selective agonists for prostaglandin receptors are being explored for the therapy of local skeletal defects,⁹² but their multiple effects on other organ systems may limit their use as skeletal anabolic agents.

Agents that inhibit resorption and stimulate formation

Most recently, strontium ranelate has been developed as an agent that is reported to inhibit bone resorption and stimulate bone formation. Its effects on bone mass are difficult to evaluate because strontium is incorporated into the mineral and alters its density. However, strontium ranelate has been shown to reduce fractures.⁹³ An exciting new approach to the possible simultaneous inhibition of resorption and stimulation of formation would be activation of the Wnt signaling pathway. An approach that is currently being explored is “disinhibition” of Wnt signaling, which can be achieved by antibodies to sclerostin.⁹⁴

Future direction

In view of the remarkable and unexpected findings of the last decade, it is hazardous to predict where the next decade will lead. Many more factors that regulate bone remodeling and influence skeletal integrity are being discovered, and studies of these factors should lead to better understanding of the pathogenesis and new approaches to therapy. An equally critical goal is to improve the application of what we already know to reversing the ever-increasing burden of osteoporotic fractures worldwide. This will require political and socioeconomic changes as well as improvements in the

distribution of medical care. Orthopedists can play an important role here — for example, developing programs that ensure that patients with fragility fractures are followed up with appropriate diagnosis and treatment and supporting and promoting efforts to improve bone health at all ages.

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